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Review

An Overview of the Potential of Medicinal Plants Used in the Development of Nutraceuticals for the Management of Diabetes Mellitus: Proposed Biological Mechanisms

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Abstract: Diabetes mellitus (DM) is a chronic metabolic disorder in which the pancreas does not produce enough insulin or the body cannot effectively use it. The prevalence of diabetes is increasing steadily, making it a global public health problem. Several serious complications are associated with this disease. There are a number of different classes of antidiabetic medications. Interestingly, traditional medicine can also be used for the development of novel classes of hypoglycemic therapeutics. This article summarizes an update of the potential of various important medicinal plants used in the development of nutraceuticals for the management of diabetes mellitus, and a proposal of their biological mechanisms.

Keywords: medicinal plants; diabetes mellitus; nutraceuticals; management; biological mechanisms

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1. Introduction

Diabetes mellitus (DM) and its management constitute a large social, financial, and health system burden across the world. The prevalence of diabetes in 2017 was estimated to be ~451 million diabetic persons (age range 18–99 years) worldwide; this figure is expected to increase to 693 million by 2045 [1]. The most common manifestation of DM is hyperglycemia [2,3]. Vascular complications of diabetes constitute the main cause of mortality in diabetic patients [4–6]. In 2017, approximately 5 million deaths worldwide were attributable to diabetes (age range 20–99 years) [1]. Type I diabetes is a result of the defects in insulin secretion caused by inherited and/or acquired deficiency in the production of insulin by the pancreas (Figure 1). Type II diabetes is a result of the ineffectiveness of insulin, caused by insulin resistance in the liver and peripheral tissues. As type II diabetes progresses, reduced β-cell mass and dysfunction, impaired insulin signaling, altered lipid metabolism, subclinical inflammation, and increased oxidative stress may take place [7,8] (Figure 1).

Diabetes causes tissue damage that may be attributed to increased oxidative stress, abnormal glucose levels, altered lipid metabolism, and subclinical inflammation [9,10]. These and other unknown mechanisms lead to additional micro- and macro-complications, such as cardiovascular complications (including angiopathy and high blood pressure), nephropathy, retinopathy, neuropathy, skin ulcers, and weight gain [5,6,9,11–13].

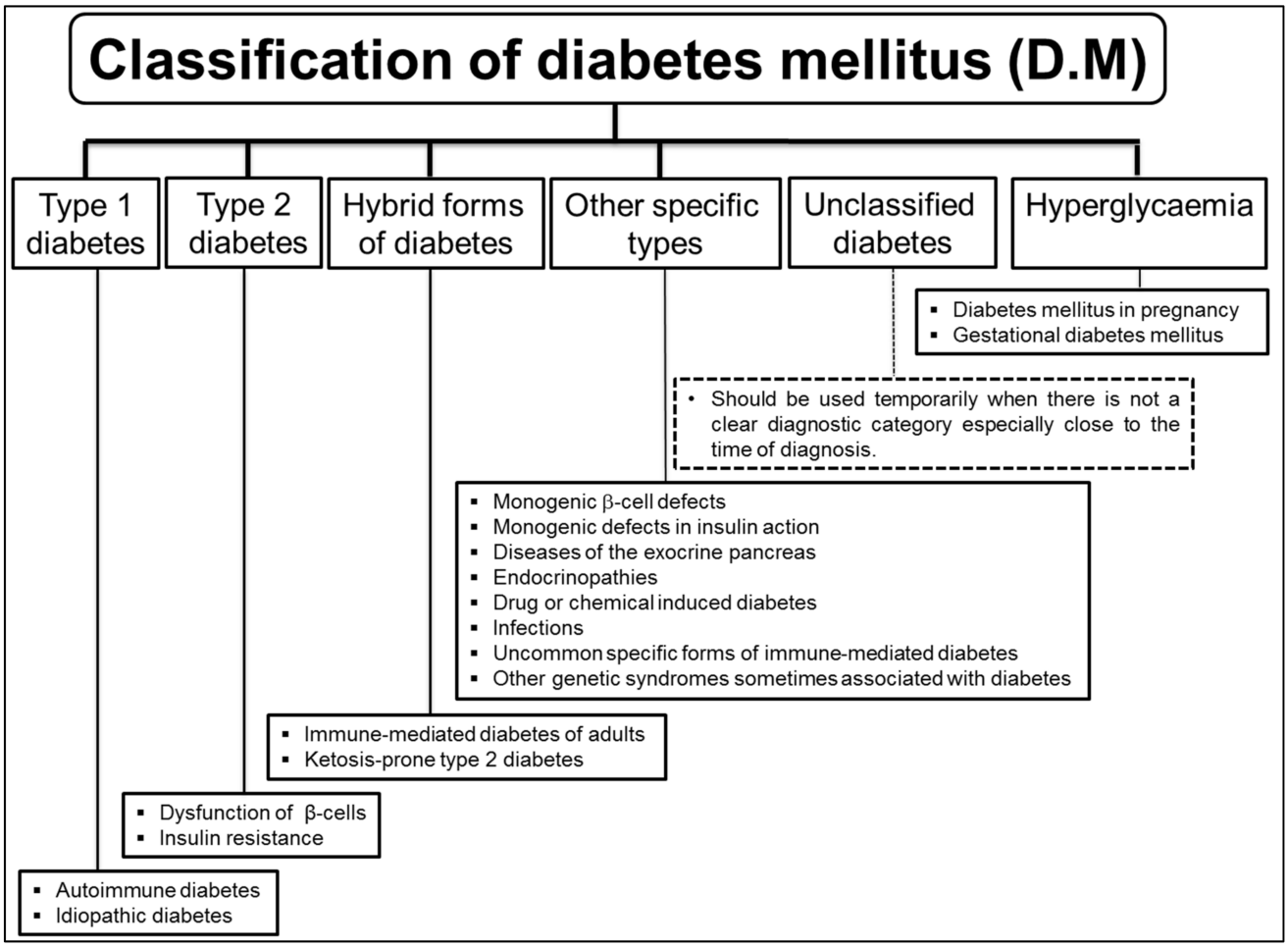


Figure 1. Classification of diabetes mellitus.

With the exception of very specific situations, clinically effective antidiabetics do not cure DM, but rather help with its management and/or prevention [14]. The available classes of antidiabetics are mainly synthetic, and are associated with high costs and numerous side effects [15]. Nevertheless, the therapeutic potential of natural remedies should be explored in the development of novel classes of hypoglycemic drugs. Historically, plants have often been considered as sources for drug development programs. Many pharmaceuticals commonly used in traditional medicine today are structurally derived from medicinal plant compounds.

According to Abbas et al. (2019) [16], medicinal plants can produce molecules that constitute potential candidates for DM treatment. These molecules act as dipeptidyl peptidase-4 enzyme, α-glucosidase enzyme, and SGLT2 inhibitors.

Jacob and Narendhirakannan (2019) [17] listed a total of 81 medicinal plants reputed for their antidiabetic, anti-hyperglycemic, hypoglycemic, anti-lipidemic and insulin-mimetic properties in their review. In another review, Gupta (2018) [18] cited active phytoconstituents isolated from 22 potent antidiabetic plants; he also mentioned the plant parts containing the active molecules that might be useful for drug development.

Natural product libraries constitute a valuable and rich source of ligands for nuclear receptors considered to be promising therapeutic agents. By uncovering the regulatory mechanisms and transcriptional targets of the peroxisome proliferator-activated receptors (PPARs) and other related receptors, it should be possible to provide a comprehensive insight into the pathogenesis of DM as a tool for rational drug design [19].

A natural screening strategy would be beneficial for antidiabetic research programs. In fact, this review highlights several known plants and their secondary metabolites that are effective in the management and control of diabetes (Table 1).

Table 1. Proposed biological mechanisms underlying the actions of medicinal plants on diabetes.

Medicinal Plants	Organs	Biological Mechanisms			Management of Diabetes and its Complications
	Liver	↑PPAR-γ	↑Glycogen synthesis ↓Gluconeogenesis	↓Hepatic glucose output	
		↑PPAR-α and PPAR-δ	↓Fatty acid synthesis ↑Fatty acid oxidation	↓Liver fats ↑Hepatic insulin sensitivity	
			↑Energy expenditure		
		↑AMPK	↓Blood glucose ↑Insulin sensitivity ↓Serum lipids		
		↓ACC	↓Blood glucose ↑Insulin sensitivity ↓Serum lipids		
	Adipocytes	↑PPAR-α and PPAR-δ	↓Fat intake, fatty acid synthesis ↑Energy expenditure		
		↑PPAR-γ, adiponectin ↑TNF-α	↑Energy expenditure ↑Insulin sensitivity, glucose uptake		
		Inhibition of AMPK Activation of Akt	↑Differentiation of adipocytes	↑Accumulation of fat	
		↑GLUT4	↓Blood glucose ↑Insulin sensitivity ↓Serum lipids		
		↑Glc uptake	↓Blood glucose ↑Insulin sensitivity ↓Serum lipids		
	Skeletal Muscle	↑PI3K and P38-MAPK	↑Insulin sensitivity, glucose uptake		
		↑Expression and allocation of GLUT4	↑Glucose uptake		
		↑Glc uptake	↓Blood glucose ↑Insulin sensitivity ↓Serum lipids		
	Pancreas	↑Insulin synthesis and secretion cellular signaling	↑Glucose clearance		
		↑β-cell regeneration	↑Glucose clearance		
	Gastrointestinal Tract	↓α-amylase and α-glucosidase	↓Absorption of glucose		

Table 1 illustrates the biological mechanisms of medicinal plants on diabetes, as well as a list of bioactive compounds involved in these mechanisms.

2. Flavonoids

Flavonoids are a large family of compounds sharing a common 15-carbon skeleton, which consists of two phenyl rings and a heterocyclic ring [20,21]; they are secondary metabolites synthesized by plants and fungi [20,21]. Flavonoids may be divided into subclasses, such as anthocyanidins (e.g., cyanidin), flavan-3-ols (e.g., catechin, epicatechin, epicatechin gallate, epigallocatechin gallate, thearubigins, proanthocyanidins, and theaflavins), flavanones (e.g., naringenin and eriodictyol), flavonols (e.g., quercetin and myricetin), and isoflavones [22] (Table 2).

Table 2. Subclasses, chemical structures, and examples of flavonoids present in plants.

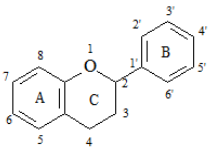
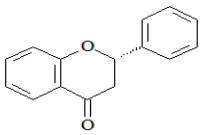
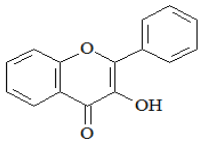
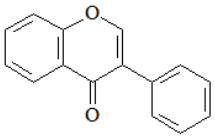
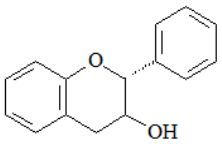
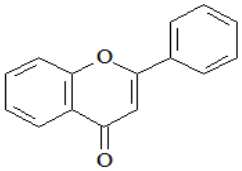
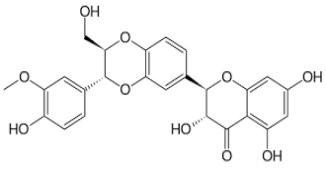
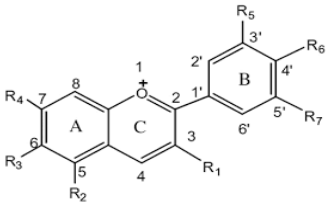
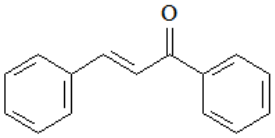
Flavonoids	Subclasses	Chemical Structure	Examples
 **Flavan (Basic Structure of Flavonoids)**	**Flavanones**		■ Naringenin ■ Eriodictyol ■ Hesperetin
	Flavonols		■ Isorhamnetin ■ Kaempferol ■ Myricetin ■ Quercetin
	Isoflavones		■ Biochanin A ■ Daidzein ■ Formononetin ■ Genistein ■ Glycitein
	Flavan-3-ols		■ Catechin ■ Epicatechin ■ Epicatechin gallate ■ Epigallocatechin gallate ■ Proanthocyanidins ■ Theaflavins ■ Thearubigins
	Flavones		■ Apigenin ■ Baicalein ■ Chrysin ■ Luteolin
	Flavonolignans		■ Silibinin ■ Silychristin ■ Silandrin

Table 2. *Cont.*

Flavonoids	Subclasses	Chemical Structure	Examples
	Anthocyanidins		■ Aurantinidin ■ Capensinidin ■ Cyanidin ■ Delphinidin ■ Europinidin ■ Hirsutidin ■ Malvidin ■ Pelargonidin ■ Peonidin ■ Petunidin ■ Pulchellidin ■ Rosinidin
	Chalcones		

Flavonoids are constituents of fruits, vegetables, and herbs, particularly found in chocolate, grapes, berries, apples, soybeans, soy foods, onions, kale, broccoli, citrus fruits, juices, and teas (especially green and white) [22]. Many beneficial effects have been attributed to flavonoids, including the improvement of vascular function and blood pressure reduction (e.g., epicatechins), improvement of insulin sensitivity (e.g., epicatechins, polyphenols) and secretion (e.g., quercetin), and platelet activity reduction (e.g., epicatechins) [23–25] (Figure 2). The antidiabetic effect of flavonoids is due to their regulation of several pathways' molecular targets, including reducing apoptosis, improving the proliferation of pancreatic β-cells, promoting insulin secretion, regulating glucose metabolism and hyperglycemia, enhancing glucose uptake in the skeletal muscle and adipose tissues, and decreasing insulin resistance [25]. Moreover, flavonoids have been shown to be beneficial for glucose homeostasis [26]. The administration of this flavonoid was also shown to attenuate fasting and postprandial blood glucose levels in diabetic mice and rats [27].

Quercetin inhibits aldolase reductase (AR) in diabetic patients; it exists in cabbage, red wine, buckwheat tea, green tea, apples, berries, onions, beans and nuts, *Ginkgo biloba*, St. John's wort, and American elder [28]. Quercetin has been reported as a natural immunity booster with α-glucosidase-inhibitory activity in vitro [29,30]. Furthermore, quercetin reduces intestinal glucose absorption by inhibiting GLUT2, and decreases lipid peroxidation; in addition, according to [24], it improves catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) levels, and stimulates GLUT4 expression in skeletal muscle.

Furthermore, the beneficial effects of hesperidin and naringin have been reported in the treatment of diabetes through the regulation of the hepatic glucose metabolic enzymes involved in glycolysis and gluconeogenesis [31]. Another flavonoid, berberine, lowers blood insulin levels by enhancing insulin sensitivity and by enhancing GLUT1 expression and promoting its activity [32,33]. Berberine also improves insulin secretion in patients with impaired β-cell function [34,35]. Apigenin-6-C-β-fucopyranoside was shown to reduce blood glucose levels and to improve insulin secretion in hyperglycemic rats [36–38]. Another flavonoid, kaempferitrin, stimulates GLUT4 translocation and synthesis in adipocytes [39–41].

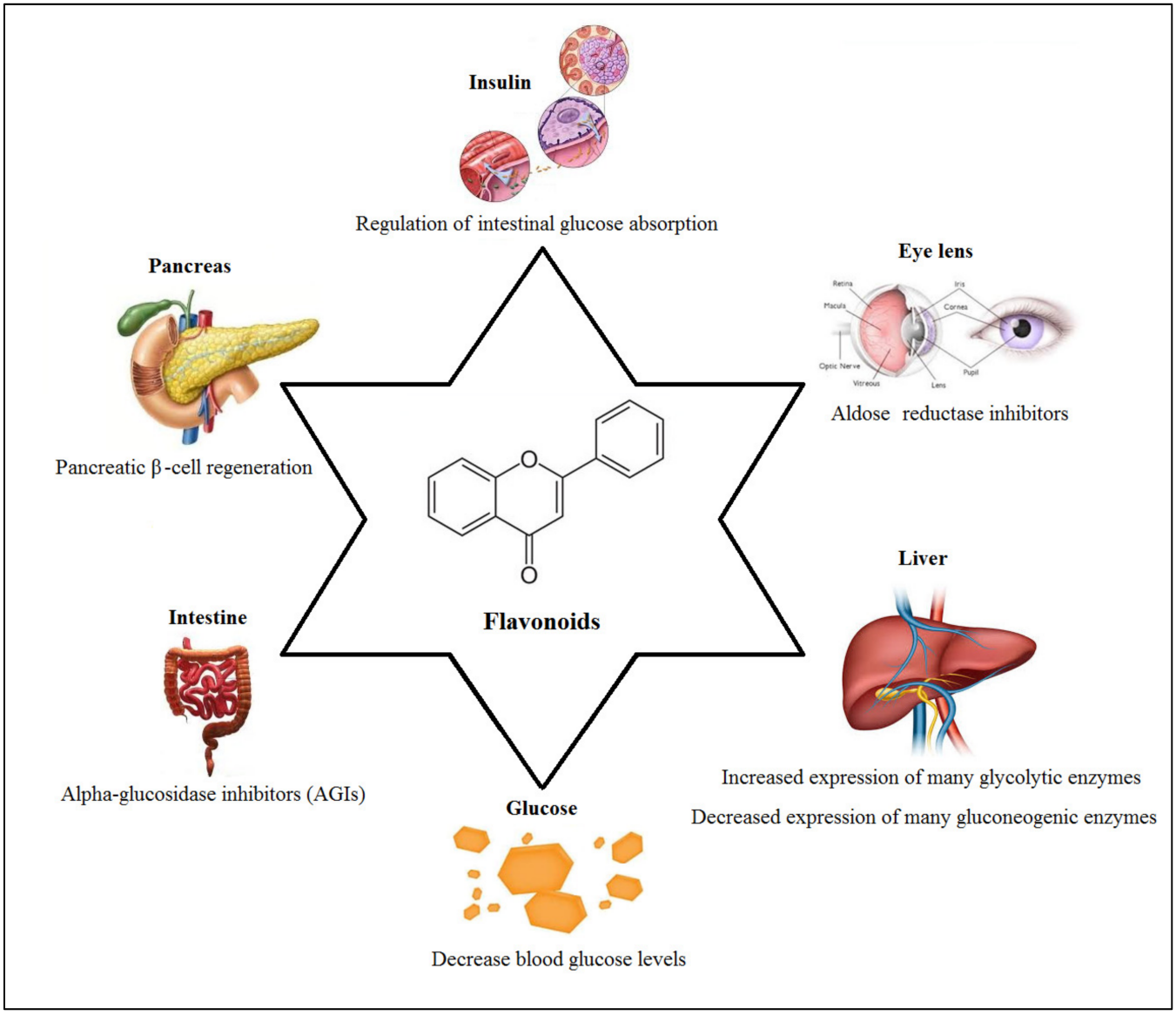


Figure 2. Mechanism of action of flavonoids on diabetes.

Naringin and hesperidin have been shown to attenuate hyperglycemia-mediated oxidative stress and the production of pro-inflammatory cytokines in high-fat diet/streptozotocin (HFD/STZ)-induced diabetic rats [42,43]. However, the anthocyanin cyanidin-3-O-β-glucoside has been reported to increase hepatic glutamate–cysteine ligase catalytic (Gclc) expression by increasing cAMP levels in order to activate protein kinase A (PKA). PKA upregulates cAMP response element-binding protein (CREB) phosphorylation to promote CREB–DNA binding and increase Gclc transcription; this results in a decrease in hepatic ROS levels and pro-apoptotic signaling [44].

Fisetin is a dietary flavonoid characterizing strawberry, apple, persimmon, grape, onion, and cucumber [45]. This molecule induced improvement in plasma insulin and antioxidant levels in diabetic rats; furthermore, Prasath et al. (2013) [46] reported that it decreased the levels of blood glucose and glycated hemoglobin (HbA1c).

Procyanidins and cyanidins found in berries improved insulin resistance and upregulated GLUT4 in obese and diabetic mice [47]. Pelargonidin decreased the levels of glucose and thiobarbituric-acid-reactive substances (TBARSs), as well as increasing SOD levels, in STZ-induced diabetic rats [48]. Citrus species contain diosmin (flavonoglycoside), which exerts proven anti-hyperglycemic activity in streptozotocin–nicotinamide-induced dia-

betic rats; in fact, it enhances the activity of some glycolytic enzymes—mainly hexokinase and glucose-6-phosphate dehydrogenase—while it inhibits the gluconeogenic enzymes glucose-6-phosphatase and fructose 1,6-bisphosphatase [49].

Moreover, preventive effects against hyperglycemia and dyslipidemia induce nephropathy, neuropathy, liver damage, and cardiovascular disorders, which have been attributed to rutin; this flavonoid is also able to inhibit the accumulation of sorbitol, ROS, and advanced glycation end-products (AGEs) [50]. In fact, the elevated levels of glucose form covalent adducts with plasma proteins through a non-enzymatic process known as glycation [51]; this glycation leads to the production of AGEs, which are associated with DM complications [52].

Rutin is believed to decrease carbohydrate absorption from the small intestine by pancreatic β-cells, to stimulate insulin secretion, and also to increase tissue glucose uptake [53]. Hesperidin reverses hyperglycemia and hyperlipidemia by downregulating free radical generation [54]. Naringenin not only inhibits intestinal α-glucosidase activity, but also restores the lipid profile changes and improves antioxidant status and hepatic function markers, as reported by Priscilla et al. (2015) [55]. Specifically, the risk of diabetes is inversely correlated with the intake of flavan-3-ols (monomers and dimmers only) and flavonol [56]. Daily supplementation of flavan-3-ols and isoflavones (dark chocolate) to type 2 diabetics significantly improved insulin sensitivity and reduced the risk of coronary heart disease in postmenopausal women [57]. Myricetin significantly ameliorates insulin resistance, in addition to exerting antioxidant, anti-inflammatory, and aldose-reductase-inhibitory actions [58]. Administration of kaempferol—an abundant flavonoid in berries, *Gingko biloba*, vegetables, and grapes—to diabetic rats reverted the levels of blood glucose, insulin, and enzymatic and non-enzymatic antioxidants [59].

2.1. Isoflavones

Flavonoids in the ethanolic extract of *Sophora flavescens* roots (*Sf*-EtOAcà) improved glucose tolerance and reduced hyperglycemia. The insulin levels were also restored in diabetic mice after treatment, further activating GLUT4 translocation, which should be modulated by the AMPK pathway [60]. Dietary intake of genistein significantly improved the lipid profile, plasma insulin, and hyperglycemia in obese diabetic mice [61].

2.2. Flavones

Apigenin was efficient in overcoming hyperglycemia, and reduced the levels of antioxidants such as SOD, CAT, and GSH in alloxan-induced diabetic rats [62]; it also enhanced GLUT4 translocation, suggesting efficacy in glucose reduction and β-cell preservation. Chrysin, which is commonly found in honey, pollen, fruits, and other medicinal herbs, was demonstrated to be able to reduce the risk of secondary complications of diabetes—such as neuropathy and nephropathy—in high-fat diet/streptozotocin-induced diabetic rats, in addition to improving insulin secretion and reducing glucose levels and lipid peroxidation [63]. Baicalein isolated from the roots of *Scutellaria baicalensis* Georgi and fruits of *Oroxylum indicum* (L.) Benth was found to significantly improve hyperglycemia, insulin levels, and glucose tolerance, in addition to lowering HbA1c levels [64]. Moreover, silybin—a constituent of milk thistle (*Silybum marianum* (L.) Gaertn)—has been demonstrated to have beneficial effects against diabetic complications—such as neuropathy and nephropathy—due to its antioxidant nature; it is also believed to have PPAR-γ agonist effects [65].

3. Saponins

Saponins are naturally occurring glycosides typically obtained from a variety of plants [66,67]. The complex structure of saponins is due to the variation in the structure of the aglycone, the nature of the side chains, and the position of attachment of these moieties on the aglycone [68] (Figure 3).

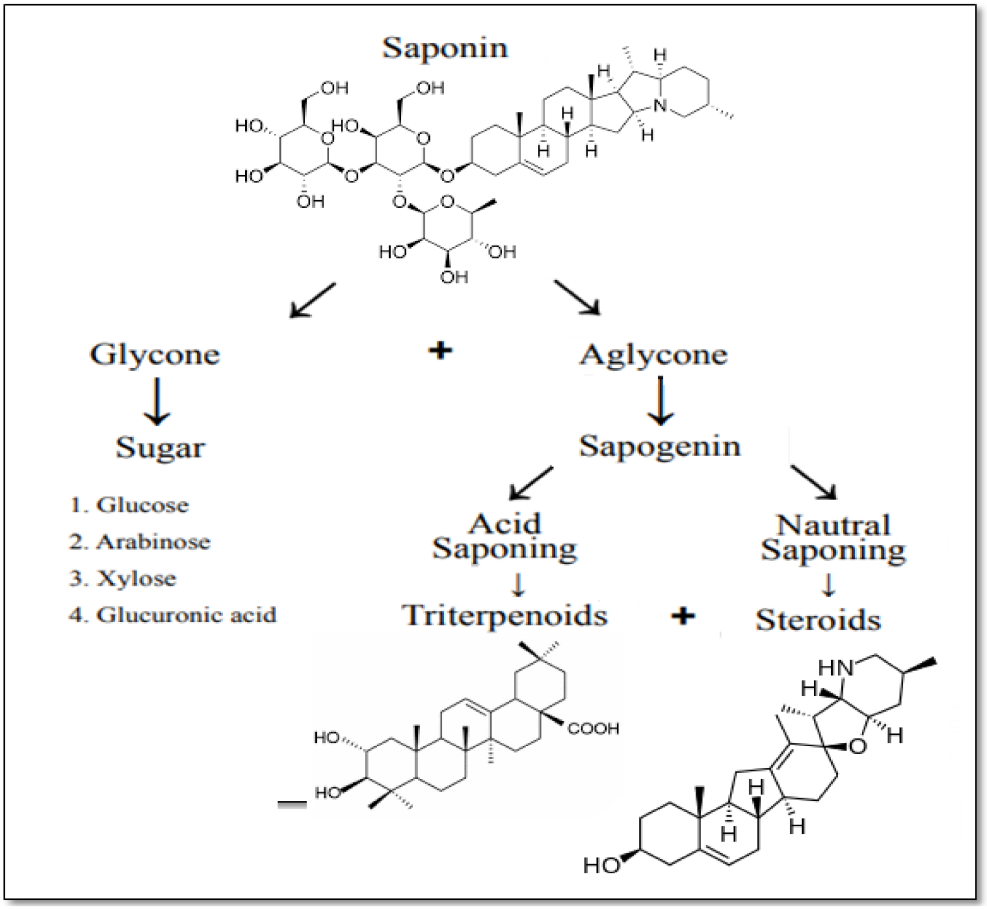


Figure 3. The complex structure of saponin and its derivatives.

Saponins have been reported to exhibit many pharmacological properties (Figure 4), including antidiabetic effects via the induction of hypoglycemia and the reduction in plasma triglyceride levels [69,70]. According to Patel et al. (2012) [71], saponins from *B. laciniosa* seeds decreased blood glucose levels in diabetic rats.

Furthermore, saponins have been shown to attenuate obesity by reducing weight gain and increasing adiponectin levels in high-fat-diet-induced obese rats [72]. Choi et al. (2017) [73] reported that saponins improve not only glucose tolerance and hypolipidemia, but also pancreatic damage; according to these authors, ginseng extracts containing saponin inhibited cytokine-induced apoptosis in the pancreatic β-cell line MIN6N8. Similarly, saponins from red ginseng (*P. ginseng*) inhibited apoptosis of pancreatic β-cells induced by cytokines [74]. These findings are in accordance with those of Kim et al. (2009) [75], who reported that another saponin from ginseng (ginsenoside Rg3) not only improved islet cell function, but also debilitated apoptosis in murine islets. On the basis of these results, it seems that the treatment of chronic diabetic rats with saponin may attenuate damage to the pancreatic islet cells.

The ability of saponin to reduce elevated plasma blood glucose makes it an excellent candidate for the treatment of diabetes mellitus. Saponins act as hypoglycemic molecules through the restoration of insulin response [76,77], improvement in insulin signaling [78], increase in plasma insulin levels, and induction of insulin release from the pancreas [79]; they are also able to inhibit disaccharide activity [80–82], gluconeogenesis [83], glucosidase activity [84], and mRNA expression of glycogen phosphorylase and glucose-6-phosphatase [85]. Saponins also increase the expression of GLUT4 [86] and activate glycogen synthesis [33].

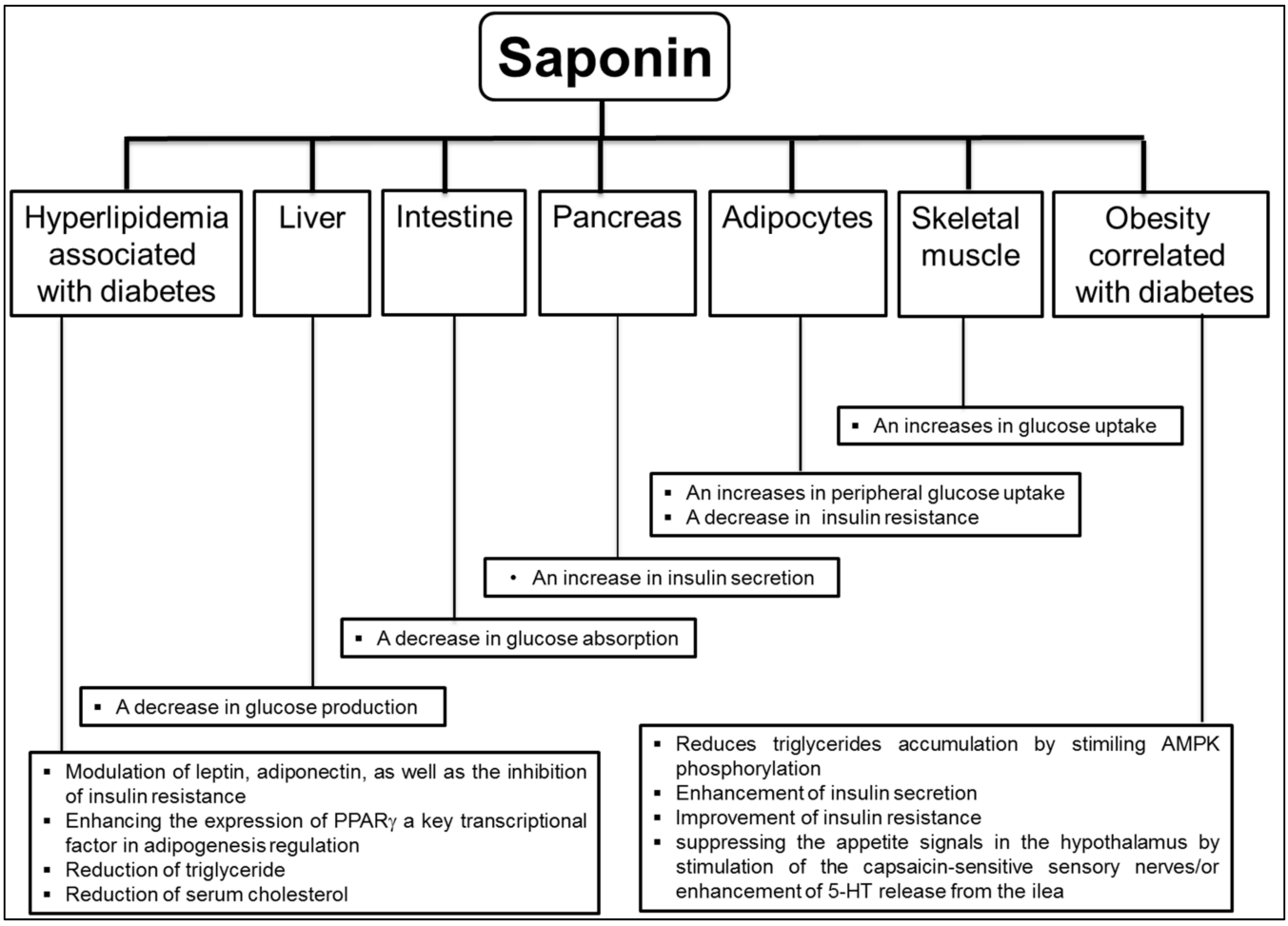


Figure 4. Properties and effects of saponins in diabetes.

Elekofehinti et al. (2014) [87] reported specific lipoprotein lipase/peroxisome proliferator-activated receptor (PPAR)-γ/phosphatidylinositide 3-kinase (PI-3-K)/protein kinase B (Akt) activation, adiponectin gene upregulation, fatty-acid-binding protein 4 repression (FABP4), and glucose transporter type 4 (GLUT4) membrane exocytosis in experimental animals following saponin treatment.

Reactive oxygen species (ROS) are a direct consequence of hyperglycemia in diabetes mellitus [88,89]. ROS are correlated with oxidative stress, which plays an important role in the initiation and progression of diabetic neuropathy [90,91]. It has been reported that saponins possess antioxidant properties in both in vitro and in vivo models [77,92,93]. These properties are due to the presence of many -OH groups in the structure of saponin. This structural particularity is responsible for the prevention of ROS formation in diabetes. Moreover, saponins can induce antioxidant enzymes such as catalase and superoxide dismutase (SOD), which are generally lowered in diabetic animal models [92,94–96]. The induction of antioxidant enzymes reduces the production of ROS in diabetes. The increase in blood glucose induces an increase in the levels of serum lipids; such an elevation represents a risk factor for coronary heart disease [97]. Saponin modulates the expression of many genes associated with lipid metabolism [98] and, consequently, regulates hyperlipidemia (through the modulation of leptin, adiponectin, etc.) and inhibits insulin resistance [98]. Saponins also act by enhancing the expression of PPAR—a key transcriptional factor in adipogenesis regulation [78,99,100]—thus reducing triglyceride levels and serum cholesterol levels [101,102].

Obesity is induced by a variety of environmental and genetic factors, and is correlated with the prevalence of diabetes and cardiovascular disease. In this context, it has been

reported that saponins from *Camellia sinensis* are able to suppress the appetite signals in the hypothalamus through the stimulation of the capsaicin-sensitive sensory nerves—probably the vagal afferent nerves—or enhancement of 5-HT release from the ilea, leading to reduced food intake and body weight gain [103]. Furthermore, platycodin saponins reduced obesity in rats by inhibiting pancreatic lipase [104]. Another study showed that glycyrrhizic acid—a triterpenoid saponin from *Glycyrrhiza glabra* roots—induced lipoprotein lipase expression in non-hepatic tissues, resulting in decreased tissue lipid deposition [105].

4. Examples of Plants with Antidiabetic Properties

4.1. Fenugrec (Trigonella Foenum-Graecum)

Diosgenin is a steroid of fenugreek that alleviates symptoms related to diabetes mellitus, and other diseases [106]. Several scholars have reported that diosgenin stabilizes insulin and glucose in induced diabetic animals. A study by Kalailingam et al. (2014) [107] showed that diosgenin decreased glycolytic enzyme glucokinase concentrations in STZ-induced diabetic rats. Following 30 days of treatment with diosgenin, an increase in the number of insulin granules and β-cells was marked in STZ-induced diabetic rats. Additionally, antioxidant enzyme concentrations, glucose-6-phosphatase, pancreatic β-cell numbers, serum HDL, alanine transaminase, glycated hemoglobin, serum LDL, and total cholesterol were stabilized following 30 days of controlled dosage of diosgenin. According to Vijayakumar et al. (2005) [108], fenugreek seed extract was commensurable with insulin in alloxan-induced diabetic mice. The fenugreek seed extract positively impacted the intraperitoneal glucose absorption in normal mice.

Fenugreek seeds contain the amino acid 4-hydroxy isoleucine, which has insulinotropic and antidiabetic properties [109,110]; this amino acid has been reported to directly stimulate pancreatic cells. The fenugreek seed owes its hypoglycemic effect to delaying gastric emptying, slowing carbohydrate absorption, inhibiting the transport of glucose, increasing the number of erythrocyte insulin receptors, and modulating the utilization of peripheral glucose [111,112].

4.2. Date Palm (Phoenix dactylifera L.)

Date palm pits and fruit extracts inhibit the activity of α–amylase—a digestive enzyme secreted from the pancreas and salivary gland [113]. α–Amylase is involved in the hydrolysis of starch/polysaccharides into disaccharides and oligosaccharides which, in turn, are broken down into glucose [113]. Inhibition of α-amylase would diminish the breakdown of starch in the gastrointestinal tract. The α-amylase inhibitors are the molecular target for oral hypoglycemic agents such as acarbose prescribed for the treatment of type II diabetes. Date palm varieties—especially the Kentichi variety—inhibit key enzymes related to diabetes and obesity. The methanol extracts of all organs had the highest activity; this result is consistent with the high phenolic and flavonoid contents. In this context, Shobana et al. (2009) [114] reported that the phenol-rich plant extracts are characterized by an important potential to inhibit the α-amylase enzyme. In fact, phenolic compounds—and especially flavonoids—are potential antidiabetics, inhibiting α-amylase activity [115].

4.3. Garlic

The hypoglycemic effects of *Bulbus allii sativi* have been demonstrated in vivo. The oral administration of an aqueous, ethanol, petroleum ether, or chloroform extract, along with garlic essential oil, lowered blood glucose levels in rabbits and rats [116–119]. Allicin administered orally to alloxan-induced diabetic rats lowered blood glucose levels and increased insulin activity in a dose-dependent manner [118]. Garlic extracts appear to enhance insulin production, while allicin seems to protect insulin against inactivation [120]. The ability of *Allium sativum* to reduce blood glucose levels has been reported in alloxan- and STZ-induced diabetic rats and mice [121]. S-allyl cysteine sulfoxide (alliin,)—a sulfur-containing amino acid in garlic—is able to reduce diabetes in rats almost to the same extent as glibenclamide and insulin [122]. The administration of garlic also reduces blood

glucose levels in a dose-dependent manner. An active ingredient (allyl propyl disulfide) in onions is reputed for its antidiabetic properties [123]. A compound called S-methyl cysteine sulfoxide (SMCS), isolated from onions, showed effects similar to those of insulin in a group of diabetic rats [124]. The hypoglycemic effect of garlic has been mainly attributed to allicin-type compounds [120,125]; it is correlated with the sulfur compounds di (2-propenyl) disulfide and 2-propenyl propyl disulfide. The mechanism of hypoglycemic action probably involves direct or indirect stimulation of insulin secretion [126]. Moreover, these disulfide compounds could have an effect of sparing insulin from -SH inactivation by reacting with endogenous thiol-containing molecules such as cysteine, glutathione, and serum albumins [127]. The garlic extract might enhance glucose utilization, since it significantly decreased the blood glucose levels in glucose-loaded rats. This fact could be justified by the potentiation of the effect of insulin due to an increase in pancreatic insulin secretion from β-cells, or its release from bound insulin.

4.4. Cumin (Cuminum cyminum)

In a glucose tolerance test conducted in rabbits, cumin significantly increased the area under the glucose tolerance curve and the hyperglycemic peak. A methanolic extract of cumin seeds reduced the blood glucose, inhibited glycosylated hemoglobin, creatinine, and blood urea nitrogen, and improved serum insulin and glycogen (liver and skeletal muscle) content in alloxan- and streptozotocin (STZ)-induced diabetic rats. Some collateral benefits—such as decreased creatinine and improved insulin production, thus preventing some microvascular complications—are implicated in the pathogenesis of diabetes. It was demonstrated that aqueous cumin extract prevented in vitro glycation Cf total soluble protein and α-crystallin, and delayed the progression and maturation of STZ-induced cataracts in rats. Protein glycation interferes with their functions by disrupting their conformation, which alters their enzymatic activity. AGEs form intra- and extracellular connections with proteins, but also with some other endogenous key molecules, such as lipids and nucleic acids, contributing to the development of diabetic complications. Protein glycation and the formation of advanced glycation end-products (AGEs) play a key role in the pathogenesis of diabetic complications, such as retinopathy [51].

Furthermore, cumin prevented the loss of chaperone activity in diabetic rats, and also attenuated the structural changes of α-crystallin in the lens [128,129]. Deepak (2013) [130] reported that caraway oil showed anti-hyperglycemic activity in alloxan-induced diabetic rats; however, no change was registered in basal plasma insulin concentration, indicating that this pharmacological activity is not associated with insulin secretion.

4.5. Olive (Olea europea L.)

Olive leaves have been widely used in traditional medicine as remedies for several diseases, especially in Mediterranean countries. Olive leaves are rich in bioactive compounds reputed for their beneficial effects in metabolic syndrome, dyslipidemia, and hypertension [131,132]. The most interesting are polyphenols, such as oleuropein (OLE), hydroxytyrosol, and tyrosol; these compounds can prevent diseases characterized by oxidative stress, such as DM [133].

Aqueous and ethanol extracts of olive leaves exert antioxidant effects in vivo, and have hypocholesterolemic proprieties [134]. In a murine diabetic model, OLE administration at concentrations of 20, 40, and 60mg/kg daily induced a significant blood glucose decrease. Olive leaf extracts containing more than 35% OLE induced a significant improvement in hyperglycemia and impairment of glucose tolerance in Tsumura Suzuki obese diabetes (TSOD) mice, according to Annunziata et al. (2018) [135]. Furthermore, OLE administration increased serum insulin levels [136].

Ranieri et al. (2019) [137] reported that OLE treatment attenuated Cd-induced actin S-glutathionylation, thereby stabilizing actin filaments. OLE may serve as a potential adjuvant against cadmium-induced nephrotoxicity, which is one of the most important DM complications.

Benlarbi et al. (2020) [138] reported that olive leaf extract and OLE could be used to prevent complications from diabetes; according to the same authors, this compound was able to protect retinal cells against the toxic effects of glucose by improving the viability of photoreceptors. Thus, olive leaf extracts could be exploited as nutraceuticals that provide health benefits mainly in the prevention and/or treatment of diabetes. Moreover, Centrone et al. (2020) [139] highlighted the importance of valorizing olive byproducts and wastewater, which can be considered as sources of bioactive compounds acting individually or synergistically to exert beneficial effects on human health.

4.6. Polysaccharides

Polysaccharides constitute a major group of organic macromolecules formed by the polymerization of simple sugar units; they are produced in plants as primary metabolites with structural and energetic roles [140]. The characteristics and metabolic behavior of polysaccharides through the mammalian digestive process explain their valuable nutritional and health effects [141].

Patel et al. (2012) [142] cited many medicinal plants with hypoglycemic potential and belonging to various families (Leguminosae, Lamiaceae, Liliaceae, Cucurbitaceae, Asteraceae, Moraceae, Rosaceae, and Araliaceae); according to the same authors, *Allium sativum*, *Gymnema sylvestre, Citrullus colocynthis*, *Trigonella foenum-graecum*, *Momordica charantia*, and *Ficus benghalensis* were the most interesting plants; their review reported some new bioactive compounds isolated from plants such as roseoside, epigallocatechin gallate, beta-pyrazol-1-ylalanine, cinchonain-Ib, leucocyanidin 3-O-β-d-galactosyl cellobioside, leucopelargonidin-3-O-α-L rhamnoside, glycyrrhetinic acid, and others that were more efficient than conventional hypoglycemic agents.

A number of in vivo studies in model systems such as mice, rats, rabbits, and humans have reported that complex polysaccharides have positive effects in decreasing the risk of hypercholesterolemia, as well as in better management of this disorder [143,144]. Consuming starches of legumes could have a positive effect on glycemia, because of the persistent effect on post-prandial glycemia, with no sudden increases. Furthermore, this may prevent both post-prandial hyperglycemia and late hypoglycemia [145]. Plant polysaccharides, through several mechanisms, act to increase the levels of serum insulin, reducing the blood glucose levels and improving glucose tolerance. It has been reported that many polysaccharides have beneficial effects in the treatment of hypoglycemia [146]. Some examples of plant polysaccharides' antidiabetic effects are given in Table 3.

Table 3. Antidiabetic effects of some plant polysaccharides.

Plant	Type of Polysaccharides	Antidiabetic Effect	Reference
Tea	Polysaccharides	High α-glucosidase-inhibitory activity in vitro and also in vivo (mice) Beneficial for hyperglycemia treatment in diabetes.	[147]
Basil seed (*Ocimum basilicum*)	Gum	Improvements in body weight, serum electrolytes, and hematological indices, along with increased pancreatic islets.	[148]
Fenugreek seeds (*Trigonella foenum-graecum* L.)	Fibers	The addition of the fiber-rich subfraction of fenugreek seeds to insulin treatment decreased hyperglycemia, glycosuria, plasma glucagon, and somatostatin levels in diabetic dogs.	[149]
Pumpkin	Protein-bound polysaccharide (PBPP)	PBPP increased serum insulin, reduced the blood glucose, and improved glucose tolerance in diabetic rats in a dose-dependent manner.	[150]
Wheat	Arabinoxylan	Postprandial glucose and insulin responses improved upon ingestion of arabinoxylan-rich fiber in human subjects.	[151]
Oatrim	β-glucan	oatrim fibers improve postprandial insulin release and glucose levels in normal and overweight persons.	[152]

Several polyherbal formulations have been tested over the years for their antidiabetic potential. In one representative study, the hypoglycemic effect of a polyherbal formulation consisting of *Tribulus terrestris*, *Piper nigrum*, and *Ricinus communis*, was established in alloxan-induced diabetic rats. Four weeks of treatment with this polyherbal formulation (100, 200 and 300 mg/kg) and glibenclamide lowered elevated blood glucose levels, which were reported to be high in diabetic controls [153]. The standard drug used was glibenclamide 10 mg/kg, and the polyherbal suspension at a dose of 400 mg/kg exhibited significant activity.

Since oxidative processes are the main cause of several metabolic diseases and age-related degenerative disorders, herbs and spices as sources of antioxidants are of great interest for the management of many diseases, such as DM [154].

Mahajan et al. (2018) [155] reported the antidiabetic effects of a polyherbal formulation containing alcoholic extract of rhizomes of *Curcuma caesia*, Roxb whole plant of *Evolvulus alsinoides*, seeds of *Citrullus lanatus*, leaves of *Gymnema sylvestre*, stems of *Tinospora cordifolia*, fruits of *Withania coagulans*, and seeds of *Caesalpinia bonduc* on normal and alloxan-induced diabetic rats, and which is mainly rich in flavonoids, triterpenoids, steroids, and alkaloids. These molecules act through increasing the insulin level or inhibiting the intestinal absorption of glucose. The administration of this polyherbal formulation may induce chemical or pharmacological interactions; according to the same authors, the weight gain and decrease in blood glucose levels were less than that achieved by the standard drug (glibenclamide 10 mg/kg). Moreover, the prepared oral polyherbal suspension was safe.

Vuksan and Sievenpiper (2005) [156] claimed that, among herbs, ginseng (Panax spp.) is the most widely used as a model to illustrate the challenges of reproducible clinical efficacy. There is no sufficient evidence to claim herbal indications for DM. There is a need for standardization in correlating herbs' composition with their efficacy.

Furthermore, various vitamins and micronutrients play significant roles in the treatment of diabetes. For example, vitamin C—or ascorbic acid—is a pre-fermented antioxidant involved in several non-enzymatic reactions. Moreover, it is a donor of electrons that efficiently scavenges free radicals (ROS) and inhibits lipid peroxidation; it also promotes regeneration of vitamin E and reduced glutathione [157]. In animals, vitamin C also reduces diabetes-induced sorbitol accumulation and lipid peroxides in erythrocytes [158].

Vitamin C supplementation impacted formamidopyrimidine DNA glycosylase (FPG) (↓20 mg/dL), and tended to reduce HbA1c levels [159]. Moreover, this supplementation also reduced total cholesterol and LDL concentrations, and tended to improve triglycerides [160].

A daily uptake of vitamin C at a dose of 1000 mg may help to prevent or reduce the development of cataracts and nerve disorders, which are serious complications of diabetes; moreover, it also inhibits protein glycosylation, associated with the development of the long-term complications associated with diabetes [161]. Considering the implication of oxidative stress in the physiopathology of DM—and especially in the pathogenesis of β-cell dysfunction—antioxidant compounds extracted from plants could be helpful in the management of diabetes and its complications [162].

Examples of plant compounds with specific effects will be mentioned as follows:

- Vanadium is found in all cells; it acts as an "insulin mimetic"; it is found in mushrooms, shellfish, black pepper, parsley, dill seed, beer, wine, and grains. According to animal and in vitro studies, vanadium has insulin-like effects in the liver, skeletal muscle, and adipose tissue [163]; moreover, it stimulates glucose uptake—either directly, or by inhibiting the phosphotyrosine phosphatase enzyme system—thus enhancing insulin receptor phosphorylation and insulin receptor (IR)–tyrosine kinase interaction [164];
- ω-3 Fatty acids, which are abundant in some plants—such as sunflower and safflower—have been reported to improve insulin resistance in animal models [165].

Despite an indirect implication in the mechanisms of diabetes, magnesium has been reported to intervene in the protection against complications of diabetes; the recommended daily intake is 1000 mg/day [166]. Complementary approaches such as the use of medicinal

plants, herbs, and/or formulations and ω-3 polyunsaturated fatty acids (PUFAs) with hypoglycemic and hypolipidemic activities can be used as alternatives to oral hypoglycemic agents (OHAs), which are reputed for their side effects [167].

- Legumes are rich in fiber, protein, and nutrients, and are slowly digested; they produce relatively small blood glucose increases. Identifying the factors determining starch digestibility may be useful in the management of diabetes and disorders of carbohydrate metabolism [168]. Centrone et al. (2020) [169] reported that mice fed with a chickpea-supplemented diet displayed lower levels of glycemia.

5. Conclusions

This review attempted to highlight the most important preventive and curative anti-hyperglycemic effects of plants and some of their constituents. All of the present data testify to the therapeutic potential of plants with antidiabetic properties, and of their constituents, which could be exploited as nutraceuticals to alleviate the symptoms of diabetes and improve quality of life. However, this strategy depends on many parameters—such as safety, long-term adverse effects, and toxicity—as well as supplementation studies and clinical trials in humans in order to prove the required positive impacts on human health.

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